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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): A1479-3P US

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

Application Number	Filed
10/714,447	November 17, 2003

First Named Inventor: Edward Roberts

Art Unit	Examiner
1624	Emily B. Bernhardt

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 48,076.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Jianzhong SHEN, Reg.#48076/
Signature

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Typed or printed name

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Telephone number

June 28, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

AstraZeneca

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Roberts, et al.	Filed: November 17, 2003
Application No.: 10/714,447	Attorney Docket No.: A1479-3P US
Arts Unit: 1624	Examiner: E. Bernhardt
Title: Novel Compounds with Analgesic Effects	

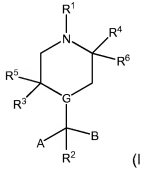
MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

ARGUMENTS ACCOMPANYING PRE-APPEAL BRIEF CONFERENCE REQUEST

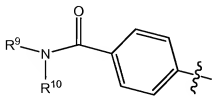
Pursuant to the Official Gazette Notices dated July 12, 2005 and February 7, 2006, Applicants hereby request a Pre-Appeal Brief Conference. A Notice of Appeal accompanies this request. This request is being filed in response to the Final Rejection dated as mailed February 16, 2006. Accordingly, a petition for two-month extension together with the requisite fees is included with this filing. Even though Applicants believe no other fees are due, Applicants hereby petition for any additional extension, and authorize that any fee for said extension or other matters related to this application be charged to Deposit Account 26-0166.

Claim 19 is pending. Claim 19 remains rejected. Briefly, the claim is directed to a compound of formula (I)



(I)

wherein G is a nitrogen atom;

A is: 

wherein the phenyl ring of the A group is optionally substituted by one or two substituents independently selected from the group consisting of CH_3, CF_3 and halogen;

R^1 is selected from the group consisting of: H; a branched or straight C_1–C_6 alkyl; –$CO(C_1$–C_6 alkyl); and (C_1–C_6 alkyl)-B' wherein B' is a C_6, C_9 or C_{10} aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C_6, C_9 or C_{10} aryl and the 5 or 6 membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH_3 or halogen;

R^2 is selected from the group consisting of H and CH_3;

R^9, and R^{10}, are selected from the group consisting of H, a branched or straight C_1–C_6 alkyl and a C_2–C_6 alkenyl;

B is an C_6, C_9 or C_{10} aromatic; or a C_6, C_9 or C_{10} hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$ and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, or 2, and wherein R^7 and R^8 are selected from: H; a branched or straight C_1–C_6 alkyl; or –$CO(C_1$–C_6 alkyl);

R^3, R^4, R^5, and R^6 are each H;

as well as pharmaceutically acceptable salts, hydrates, isoforms and isomers, other than positional isomers, thereof. The compound may be useful in binding delta opioid receptors and treating pain.

In the Final Office Action, claim 19 was rejected under 35 U.S.C. § 103 (a) over Calderon and Bilsky References in view of Chang et al. (PCT Publication WO93/15062 or U.S. Pat. No. 5,658,908, applied as of its § 102(e) date). Applicants respectfully appeal the rejection for the following reasons.

First of all, Applicants submit that there is no motivation to combine Calderon and Bilsky References with Chang et al because Chang et al. and the Calderon reference expressly teach away.

The Calderon and Bilsky References only disclose compounds with dimethyl groups on the central piperazine ring. In contrast, the compounds of claim 19 require an unsubstituted central piperazine ring (with R3-6 being all hydrogen). In fact, in all of the four Calderon and Bilsky references (cited as C1, C2, C4 and C5 in Applicants' IDS), all of the disclosed examples contain dimethyl groups on the central piperazine rings, which implies the importance of the dimethyl substitution. Furthermore, in one Calderon reference (cited as C5 in the IDS, See J. Med. Chem., Vol. 40, at Page 696, the bottom portion of the first column with a heading of "Chemistry," 1997), Calderon et al. even expressly emphasized the importance of using a dimethyl substituted immediate, which is chiral because of the dimethyl substitution, in synthesizing the dimethyl substituted final product. Had there not been a dimethyl group on the piperazine ring, the intermediate used in the Calderon reference would have been achiral and the resulting products would not have been readily separable and optically pure. Therefore, to combine the Calderon reference with Chang et al. in a way proposed by the Examiner to eliminate the dimethyl substitution would defeat one of the key advantages emphasized by Calderon et al. In conclusion, for this reason alone, Applicants submit that there is no motivation to combine the Calderon and Bilsky references with Chang et al. in the way as suggested by the Examiner.

Applicants further submit that claim 19 is unobvious over Calderon and Bilsky references in view of Chang et al. because Chang et al expressly teaches away from claim 19. A prior art that teaches away from claimed invention is a significant factor to be considered in determining obviousness. MPEP §2146.1. References cannot be combined where references teaches away from their combination. MPEP §2146.2. In addition, a prior art reference must be considered in its entirety, including disclosures that teach away from the claims. MPEP §2141.02

In this case, Chang et al. teaches that it is important to have the substitution on the piperazine ring to achieve the desired property. See page 60 of the comments made during a response by Chang et al. on February 9, 1996 (a rule 132 declaration filed by Chang et al.) during the prosecution of Chang et al., copies of the relevant pages were made of record in Applicants' previous response. In Chang et al.'s response, Chang et al. made the following statements:

> Specially, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, *show a general trend in which the substituted compounds have significantly greater opioid activity*. (Emphasis added).

The file wrapper is a considered an integrated part of Chang et al. A person skilled person reading Chang et al. as a whole would be motivated to combine Chang et al. and Calderon and Bilsky references in such a way that it would not arrive at the present invention because the skilled person would retain the methyl groups on the piperazine ring as specifically taught by Chang et al. Therefore, the motivation to combine Chang et al. and Calderon and Bilsky references to arrive at the present invention is lacking for this reason and claim 19 is unobvious over Chang et al. and Calderon and Bilsky references for this additional reason.

Applicants further submit that there is no motivation in the prior art to modify Chang et al. to arrive at the present invention.

A person reading Chang et al. as a whole will be led to believe that to achieve an optimal delta receptor binding activity, the central piperazine ring must be substituted, and thus, would not be motivated to modify Chang et al. to arrive at the present invention, which contains no substitution on the piperazine ring. In numerous occasions, Chang et al. teaches that the preferred compounds (col. 6 of U.S. Pat. No. 5,658,908) of Chang et al. to bind delta opioid receptors requires at least one of R3, R4 and R5 to be methyl (see also ln. 38, col.5; ln. 54-55, col. 6; ln.14, col.7; ln. 52, col. 19; ln. 15, col. 22; ln. 10, col. 24; and claim 1 of Chang et al). In addition, Chang et al. disclosed 92 working examples of compounds (see Examples 1-92) that were believed to be effective in binding delta receptors. However, all these compounds contain one or more methyl groups on their piperazine rings. It would be reasonable for a person of ordinary skill to believe that the one or more methyl groups on the piperazine rings are critical in achieving the desirable delta receptor binding activity. In contrast, compounds of the instant claim 19 do not contain any methyl on the piperazine ring. Therefore, an ordinary skilled person reading Chang et al would not be motivated to modify Chang et al. to arrive at the present invention and the instant claim 19 is not obvious in view of Chang et al. for this additional reason.

In summary, Applicants respectfully submit that the Office made clear errors and/or omitted one or more essential elements needed to establish a *prima facie* rejection and reversal of the rejection is respectfully requested.

Respectfully submitted,

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